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2 page(s) will be printed.

Record: 7

Title: Distribution and excretion of venlafaxine and O-***desmethylvenlafaxine*** in human milk.

Author(s): Ilett KF; Hackett LP; Dusci LJ; Roberts MJ; Kristensen JH; Paech M; Groves A; Yapp P

Author's Address: Department of Pharmacology, University of Western Australia, Nedlands.

Source: British journal of clinical pharmacology [Br J Clin Pharmacol] 1998 May; 45 (5), pp. 459-62.

Pub. Type: Clinical Trial; Journal Article

Language: English

Journal Info: *Country of Publication:* ENGLAND *NLM ID:* 7503323 *ISSN:* 0306-5251 *Citation Subsets:* IM

MeSH Heading: Breast Feeding*
Antidepressive Agents/*pharmacokinetics
Cyclohexanols/*pharmacokinetics
Milk, Human/*chemistry

Adult. Antidepressive Agents/analysis. Area Under Curve. Chromatography, High Pressure Liquid. Cyclohexanols/analysis. Female. Human. Infant. Infant, Newborn. Milk, Human/metabolism. Support, Non-U.S. Gov't. Tissue Distribution.

Abstract: AIMS: To characterise the transfer of venlafaxine (V) and its O-desmethyl metabolite (ODV) into human milk by measuring milk/plasma (M/P) ratio, and to estimate the likely dose received by a breast-fed infant. METHODS: Milk and plasma samples were collected from three lactating women who were taking venlafaxine for ***depression***, and were at steady-state. In two of the patients, venous blood and milk samples were collected ***0***, 1, 2, 3, 4, 6, 8 and 12 h post dose, while in the third patient a single pair of blood and milk samples was obtained ***0***.83 h post dose. A plasma sample was obtained from each of their infants. V and ODV were measured in plasma and milk by high performance liquid chromatography. M/P was calculated and infant dose estimated as drug concentration in milk x a milk intake of ***0***.15 l kg(-1) day(-1), relative to the weight-adjusted maternal dose. RESULTS: Mean M/P for V was 4.1 (range 2.8-4.8) and 3.1 for ODV (range 2.8-3.8). The mean total infant dose (as V equivalents) was 7.6% (range 4.7-9.2%) of the maternal weight-adjusted dose, with approximately equal amounts of V (3.5%) and ODV (4.1%) in the dose. ODV (median 100 microg l(-1)) was detected in the plasma of all three infants. The infants were healthy and showed no acute adverse effects. CONCLUSIONS: These preliminary data show that the total dose of V and ODV ingested by breast-fed infants can be as high as 9.2% of maternal intake. Moreover there were measurable concentrations of ODV in the infants' plasma. We recommend that exposed infants should be observed closely.

CAS Registry No.: 0 (Antidepressive Agents)
0 (Cyclohexanols)
93413-62-8 (O-desmethylvenlafaxine)
93413-69-5 (venlafaxine)

Revision Date: 20001218

Entry Date(s): *Date Created:* 19980901 *Date Completed:* 19980901

Citation ID(s): *PMID:* 9643618 *Medline UI:* 98305771

Database: MEDLINE

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CAPLUS ONLINE PRINTOUT

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(FILE 'HOME' ENTERED AT 07:09:05 ON 30 JUN 2002)

FILE 'REGISTRY' ENTERED AT 07:09:24 ON 30 JUN 2002
E O-DESMETHYLVENLAFAXINE/CN
L1 1 S E3

FILE 'CAPLUS' ENTERED AT 07:10:10 ON 30 JUN 2002
L2 59 S L1
L3 67081 S DEPRESSION OR HYPERACTIVITY OR ATTENTION DEFICIT
L4 11 S L3 AND L2

=> d bib abs kwic 1-11

L4 ANSWER 1 OF 11 CAPLUS COPYRIGHT 2002 ACS
AN 2002:310162 CAPLUS
DN 136:395834
TI Combining bupropion SR with venlafaxine, paroxetine, or fluoxetine: A preliminary report on pharmacokinetic, therapeutic, and sexual dysfunction effects
AU Kennedy, Sidney H.; McCann, Sonia M.; Masellis, Mario; McIntyre, Roger S.; Raskin, Joel; McKay, Gordon; Baker, Glen B.
CS Centre for Addiction and Mental Health, and the Department of Psychiatry, University of Toronto, Toronto, ON, Can.
SO Journal of Clinical Psychiatry (2002), 63(3), 181-186
CODEN: JCLPDE; ISSN: 0160-6689
PB Physicians Postgraduate Press, Inc.
DT Journal
LA English
AB This study was designed to evaluate the effect of combining bupropion sustained release (SR) with venlafaxine, paroxetine, or fluoxetine in patients who reported unacceptable sexual dysfunction when treated with monotherapy with the latter 3 agents. Following a min. of 6 wk of antidepressant treatment with a selective serotonin reuptake inhibitor (SSRI) or venlafaxine (a serotonin-norepinephrine reuptake inhibitor), eligible subjects received a further 8 wk of monitored combination therapy with bupropion SR at a dose of 150 mg/day with no alterations to index antidepressant dosing. There was a clin. significant benefit in 14 (78%) of 18 partial responders or nonresponders, and 33% (N = 6) achieved a full response (.chi.2 = 8.06, df = 2, p =.017). Sexual dysfunction, particularly a decrease in orgasmic delay, was also significantly improved with combination therapy (men: paired t = -2.1, df = 6, p =.08; women: paired t = -3.0, df = 7, p =.02). Plasma monitoring of drugs and their metabolites revealed a statistically significant increase in venlafaxine levels (F = 6.89, df = 4,24; p =.001) accompanied by a decrease in O-desmethyl-venlafaxine (F = 14.26; df = 4,24; p <.0005) during combined treatment with bupropion SR. There were no statistically significant changes in plasma levels of SSRIs (paroxetine and fluoxetine) during the trial. Bupropion had an effect on the pharmacokinetics of venlafaxine but not those of the SSRIs. Further investigation of combination treatments under randomized, double-blind conditions is recommended.
RE.CNT 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT
ST antidepressant bupropion venlafaxine paroxetine fluoxetine **depression** anorgasmia sexual dysfunction; bupropion SR venlafaxine metabolite desmethylvenlafaxine pharmacokinetic drug interaction **depression**
IT Mental disorder
(**depression**, major; bupropion SR with venlafaxine, paroxetine, or fluoxetine in sexual dysfunction patients with previous monotherapy treatment)

CAPLUS ONLINE PRINTOUT

IT 54910-89-3, Fluoxetine 61869-08-7, Paroxetine **93413-62-8**, O-Desmethylvenlafaxine 93413-69-5, Venlafaxine
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(bupropion SR with venlafaxine, paroxetine, or fluoxetine in sexual dysfunction patients with previous monotherapy treatment)

L4 ANSWER 2 OF 11 CAPLUS COPYRIGHT 2002 ACS
AN 2002:111809 CAPLUS
DN 136:288525
TI Distribution of venlafaxine and its O-desmethyl metabolite in human milk and their effects in breastfed infants
AU Ilett, Kenneth F.; Kristensen, Judith H.; Hackett, L. Peter; Paech, Michael; Kohan, Rolland; Rampono, Jonathan
CS Department of Pharmacology, University of Western Australia, Nedlands, 6009, Australia
SO British Journal of Clinical Pharmacology (2002), 53(1), 17-22
CODEN: BCPHBM; ISSN: 0306-5251
PB Blackwell Science Ltd.
DT Journal
LA English
AB Aims: To characterize milk/plasma (M/P) ratio and infant dose, for venlafaxine (V) and its O-desmethyl metabolite (ODV), in breastfeeding women taking venlafaxine for the treatment of **depression**, and to det. the plasma concn. and effects of these drugs in their infants. Methods: Six women (mean age 34.5 yr, mean wt. 84.3 kg) taking venlafaxine (median dose 244 mg day-1, range 225-300 mg day-1) and their seven infants (mean age 7.0 mo, mean wt. 7.3 kg) were studied. V and ODV in plasma and milk were measured by high-performance liq. chromatog. over a 12 h dose interval at steady-state. Infant exposure was estd. as the product of estd. milk prodn. rate (0.15 l kg-1 day-1) and av. drug concn. in milk, normalized to body wt. and expressed as a percentage of the wt.-adjusted maternal dose. Results: Mean M/PAUC values of 2.5 (range 2.0-3.2) and 2.7 (range 2.3-3.2) were calcd. for V and ODV, resp. The mean max. concns. (95% CI) of V and ODV in milk were 1161 (95% CI, 588, 1734) .mu.g l-1 and 796 (362, 1230) .mu.g l-1. Mean infant exposure was 3.2% (1.7, 4.7%) for V and 3.2% (1.9, 4.9%) for ODV (as V equiv.). V was detected in the plasma of one out of seven infants studied (5 .mu.g l-1), while ODV was detected in four of the infants, at concns. ranging from 3 to 38 .mu.g l-1. All of the infants in the study were healthy, as reported by their mothers and/or by clin. examn. on the study day. Conclusions: The concns. of V and ODV in breast milk were 2.5 and 2.7 times those in maternal plasma. The mean total drug exposure (as venlafaxine equiv.) of the breastfed infants was 6.4% (5.5-7.3%), which is below the 10% notional level of concern. There were no adverse effects in any of the infants. The data support the use of V in breastfeeding. Nevertheless, since low concns. of ODV were detected in the plasma of four out of the seven infants studied, we recommend breastfed infants should be monitored closely. Each decision to breast feed should be made as an individual risk:benefit anal.
RE.CNT 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT
AB Aims: To characterize milk/plasma (M/P) ratio and infant dose, for venlafaxine (V) and its O-desmethyl metabolite (ODV), in breastfeeding women taking venlafaxine for the treatment of **depression**, and to det. the plasma concn. and effects of these drugs in their infants. Methods: Six women (mean age 34.5 yr, mean wt. 84.3 kg) taking venlafaxine (median dose 244 mg day-1, range 225-300 mg day-1) and their seven infants (mean age 7.0 mo, mean wt. 7.3 kg) were studied. V and ODV in plasma and milk were measured by high-performance liq. chromatog. over a 12 h dose interval at steady-state. Infant exposure was estd. as the product of

estd. milk prodn. rate (0.15 l kg-1 day-1) and av. drug concn. in milk, normalized to body wt. and expressed as a percentage of the wt.-adjusted maternal dose. Results: Mean M/PAUC values of 2.5 (range 2.0-3.2) and 2.7 (range 2.3-3.2) were calcd. for V and ODV, resp. The mean max. concns. (95% CI) of V and ODV in milk were 1161 (95% CI, 588, 1734) .mu.g l-1 and 796 (362, 1230) .mu.g l-1. Mean infant exposure was 3.2% (1.7, 4.7%) for V and 3.2% (1.9, 4.9%) for ODV (as V equiv.). V was detected in the plasma of one out of seven infants studied (5 .mu.g l-1), while ODV was detected in four of the infants, at concns. ranging from 3 to 38 .mu.g l-1. All of the infants in the study were healthy, as reported by their mothers and/or by clin. examn. on the study day. Conclusions: The concns. of V and ODV in breast milk were 2.5 and 2.7 times those in maternal plasma. The mean total drug exposure (as venlafaxine equiv.) of the breastfed infants was 6.4% (5.5-7.3%), which is below the 10% notional level of concern. There were no adverse effects in any of the infants. The data support the use of V in breastfeeding. Nevertheless, since low concns. of ODV were detected in the plasma of four out of the seven infants studied, we recommend breastfed infants should be monitored closely. Each decision to breast feed should be made as an individual risk:benefit anal.

ST antidepressant venlafaxine metabolite desmethylvenlafaxine **depression** pharmacokinetics bioavailability; efexor extended release antidepressant pharmacokinetics human milk infant

IT Mental disorder
(**depression**; venlafaxine (Efexor) and metabolite O-desmethylvenlafaxine distribution in human milk and effect in breastfed infants)

IT **93413-62-8**, O-Desmethylvenlafaxine 93413-69-5, Venlafaxine 99300-78-4, Efexor
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(venlafaxine (Efexor) and metabolite O-desmethylvenlafaxine distribution in human milk and effect in breastfed infants)

L4 ANSWER 3 OF 11 CAPLUS COPYRIGHT 2002 ACS
AN 2001:389518 CAPLUS
DN 135:282600
TI Use of vancomycin silica stationary phase in packed capillary electrochromatography. II. Enantiomer separation of venlafaxine and O-desmethylvenlafaxine in human plasma
AU Fanali, S.; Rudaz, S.; Veuthey, J.-L.; Desiderio, C.
CS Area della Ricerca di Roma, Consiglio Nazionale delle Ricerche, Istituto di Cromatografia, Rome, Monterotondo Scalo, 00016, Italy
SO Journal of Chromatography, A (2001), 919(1), 195-203
CODEN: JCRAEY; ISSN: 0021-9673
PB Elsevier Science B.V.
DT Journal
LA English
AB A capillary electrochromatog. method, using vancomycin chiral stationary phase packed capillary, was optimized for the simultaneous chiral sepn. of the antidepressant drug venlafaxine and its main active metabolite O-desmethylvenlafaxine. Simultaneous baseline enantiomeric sepn. of the two compds. was obtained using a mobile phase composed of 100 mM ammonium acetate buffer pH 6/water/acetonitrile (5:5:90, vol./vol.). The electrokinetic injection for sample introduction provided a limit of quantitation for both the compds. of 0.05 .mu.g/mL racemate concn. suitable for the anal. of venlafaxine and metabolite in biol. samples. The acetonitrile mobile phase concn. was found to modulate the analytes elution times, the enantiomeric resoln. and the efficiency of the sepn. The column was tested for repeatability and linearity showing RSD values (%) in the range of 0.13-0.24, 2.47-3.66 and 1.35-2.50 for migration time,

sample/internal std. peak area ratio and enantiomeric resoln., resp. and correlation coeffs. higher than 0.9990. The method was applied to the anal. of clin. samples of patients under **depression** therapy showing a stereoselective metab. for venlafaxine.

RE.CNT 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

AB A capillary electrochromatog. method, using vancomycin chiral stationary phase packed capillary, was optimized for the simultaneous chiral sepn. of the antidepressant drug venlafaxine and its main active metabolite O-desmethylvenlafaxine. Simultaneous baseline enantiomeric sepn. of the two compds. was obtained using a mobile phase composed of 100 mM ammonium acetate buffer pH 6/water/acetonitrile (5:5:90, vol./vol.). The electrokinetic injection for sample introduction provided a limit of quantitation for both the compds. of 0.05 .mu.g/mL racemate concn. suitable for the anal. of venlafaxine and metabolite in biol. samples. The acetonitrile mobile phase concn. was found to modulate the analytes elution times, the enantiomeric resoln. and the efficiency of the sepn. The column was tested for repeatability and linearity showing RSD values (%) in the range of 0.13-0.24, 2.47-3.66 and 1.35-2.50 for migration time, sample/internal std. peak area ratio and enantiomeric resoln., resp. and correlation coeffs. higher than 0.9990. The method was applied to the anal. of clin. samples of patients under **depression** therapy showing a stereoselective metab. for venlafaxine.

IT **93413-62-8**, O-Desmethylvenlafaxine
RL: BSU (Biological study, unclassified); MFM (Metabolic formation); PEP (Physical, engineering or chemical process); PRP (Properties); BIOL (Biological study); FORM (Formation, nonpreparative); PROC (Process)
(use of vancomycin silica stationary phase in packed capillary electrochromatog. for enantiomer sepn. of venlafaxine and O-desmethylvenlafaxine in human plasma)

L4 ANSWER 4 OF 11 CAPLUS COPYRIGHT 2002 ACS
AN 2000:708682 CAPLUS
DN 134:247114
TI Lithium augmentation of venlafaxine: An open-label trial
AU Hoencamp, Erik; Haffmans, P. M. Judith; Dijken, Wim A.; Huijbrechts, Irma P. A. M.
CS Parnassia, Psycho-Medical Centre, The Hague, Neth.
SO Journal of Clinical Psychopharmacology (2000), 20(5), 538-543
CODEN: JCPYDR; ISSN: 0271-0749
PB Lippincott Williams & Wilkins
DT Journal
LA English
AB The authors conducted an open-label study of the efficacy and tolerability of venlafaxine and of lithium augmentation in outpatients with **depression** who were not responding to venlafaxine. Outpatients aged 18 to 70 yr were eligible if they had a min. baseline score of 16 on the 17-item Hamilton Rating Scale for **Depression** (HAM-D). Patients were started on venlafaxine 37.5 mg twice daily for 1 wk. For weeks 2 through 4, the dose of venlafaxine was increased to 75 mg twice daily, and for weeks 5 through 7, the dose was further increased to 75 mg three times daily. At the end of the 7-wk treatment period, patients with a <50% decrease in their HAM-D scores from baseline were given lithium carbonate 600 mg once daily. The dose of lithium carbonate was adjusted to maintain plasma levels in the range of 0.6 to 1.0 mmol/mL. Efficacy was assessed with the 17-item HAM-D, Montgomery-Asberg **Depression** Rating Scale, and the Clin. Global Impressions Scale. Data were analyzed on an intent-to-treat basis. At the end of the 7-wk treatment period, 35% of patients showed a .gtoreq.50% decrease in their HAM-D scores from baseline. Lithium augmentation was initiated in 23 patients. The results showed that the addn. of lithium was well-tolerated and led to a further decrease in the HAM-D scores, with eight patients responding and two of

them presenting a remission. The addn. of lithium to venlafaxine was found to be a well-tolerated strategy in treatment-resistant patients.

RE.CNT 24 THERE ARE 24 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

AB The authors conducted an open-label study of the efficacy and tolerability of venlafaxine and of lithium augmentation in outpatients with **depression** who were not responding to venlafaxine. Outpatients aged 18 to 70 yr were eligible if they had a min. baseline score of 16 on the 17-item Hamilton Rating Scale for **Depression** (HAM-D). Patients were started on venlafaxine 37.5 mg twice daily for 1 wk. For weeks 2 through 4, the dose of venlafaxine was increased to 75 mg twice daily, and for weeks 5 through 7, the dose was further increased to 75 mg three times daily. At the end of the 7-wk treatment period, patients with a <50% decrease in their HAM-D scores from baseline were given lithium carbonate 600 mg once daily. The dose of lithium carbonate was adjusted to maintain plasma levels in the range of 0.6 to 1.0 mmol/mL. Efficacy was assessed with the 17-item HAM-D, Montgomery-Asberg **Depression** Rating Scale, and the Clin. Global Impressions Scale. Data were analyzed on an intent-to-treat basis. At the end of the 7-wk treatment period, 35% of patients showed a .gtoreq.50% decrease in their HAM-D scores from baseline. Lithium augmentation was initiated in 23 patients. The results showed that the addn. of lithium was well-tolerated and led to a further decrease in the HAM-D scores, with eight patients responding and two of them presenting a remission. The addn. of lithium to venlafaxine was found to be a well-tolerated strategy in treatment-resistant patients.

IT Antidepressants
Drug resistance
(lithium augmentation of venlafaxine for treatment of **depression** in humans)

IT 7439-93-2, Lithium, biological studies 93413-69-5, Venlafaxine
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(lithium augmentation of venlafaxine for treatment of **depression** in humans)

IT **93413-62-8**, O-Desmethylvenlafaxine
RL: BPR (Biological process); BSU (Biological study, unclassified); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative); PROC (Process)
(lithium augmentation of venlafaxine for treatment of **depression** in humans)

L4 ANSWER 5 OF 11 CAPLUS COPYRIGHT 2002 ACS
AN 2000:384124 CAPLUS
DN 133:17270
TI Preparation of (-)-venlafaxine and derivatives as neuronal monoamine reuptake inhibitors.
IN Jerussi, Thomas P.; Senanayake, Chrisantha H.
PA Sepracor Inc., USA
SO PCT Int. Appl., 45 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2000032556	A1	20000608	WO 1999-US28303	19991201

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK,

SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

	US 6342533	B1	20020129	US 1999-450690	19991130
	EP 1135359	A1	20010926	EP 1999-968056	19991201

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO

PRAI	US 1998-110488P	P	19981201
	US 1999-450690	A	19991130
	WO 1999-US28303	W	19991201

AB A pharmaceutical compn. comprising (-)-venlafaxine deriv. substantially free of (+)-stereoisomer is claimed. Thus, (.+-.)-venlafaxine in THF was added to a mixt. prepd. from Ph2PH and BuLi in THF at 0.degree. followed by stirring and overnight reflux to give 73.8% (.+-.)-O-desmethylvenlafaxine, which was resolved using di-p-toluoyl-L-tartaric acid to give (-)-O-desmethylvenlafaxine. Drug formulations contg. the latter are given.

RE.CNT 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

IT Mental disorder
(**attention deficit** disorder, treatment; prepn. of (-)-venlafaxine and derivs. as neuronal monoamine reuptake inhibitors)

IT **93413-62-8P** 93413-69-5P 93413-76-4P 93413-77-5P 93413-90-2P 99300-78-4P 130198-05-9P 149289-29-2P 149289-30-5P 272788-00-8P 272788-02-0P 272788-07-5P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. of (-)-venlafaxine and derivs. as neuronal monoamine reuptake inhibitors)

L4 ANSWER 6 OF 11 CAPLUS COPYRIGHT 2002 ACS
AN 2000:384122 CAPLUS
DN 133:30575
TI Preparation of derivatives of (+)-venlafaxine as inhibitors of neuronal monoamine reuptake.
IN Jerussi, Thomas P.; Senannayake, Chrisantha H.
PA Sepracor Inc., USA
SO PCT Int. Appl., 47 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2000032555	A1	20000608	WO 1999-US28306	19991201

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

	US 6197828	B1	20010306	US 1999-450691	19991130
	EP 1135358	A1	20010926	EP 1999-965065	19991201

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI

PRAI	US 1998-110486P	P	19981201
	US 1999-450691	A	19991130

WO 1999-US28306 W 19991201

AB A method of treating an affective disorder comprises administration of a (+)-venlafaxine deriv. substantially free of the (-)-enantiomer. Thus, (.+-.)-venlafaxine (prepn. given) was added to a 0.degree. mixt. of Ph2PH and BuLi followed by stirring and reflux overnight to give 73.8% (.+-.)-O-desmethylvenlafaxine, which was resolved to give (+)-O-desmethylvenlafaxine. Drug formulations contg. the latter are given.

RE.CNT 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

IT Mental disorder
(**attention deficit** disorder, treatment; prepn. of derivs. of (+)-venlafaxine as inhibitors of neuronal monoamine reuptake)

IT **93413-62-8P** 93413-69-5P, (.+-.)-Venlafaxine 93413-76-4P 93413-77-5P 93413-90-2P 99300-78-4P 130198-05-9P 149289-29-2P 149289-30-5P 272788-00-8P 272788-02-0P 272788-07-5P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. of derivs. of (+)-venlafaxine as inhibitors of neuronal monoamine reuptake)

L4 ANSWER 7 OF 11 CAPLUS COPYRIGHT 2002 ACS
AN 2000:279486 CAPLUS
DN 132:288295
TI Venlafaxine serum levels and CYP2D6 genotype
AU Veefkind, Adrian H.; Haffmans, P. M. Judith; Hoencamp, Erik
CS Zon and Schild Psychiatric Center, Amersfoort, 3800 DB, Neth.
SO Therapeutic Drug Monitoring (2000), 22(2), 202-208
CODEN: TDMODV; ISSN: 0163-4356
PB Lippincott Williams & Wilkins
DT Journal
LA English

AB Thirty-three patients with **depression** treated with 225 mg venlafaxine were genotyped for the polymorphic enzyme, debrisoquine 4-hydroxylase (CYP2D6). The relationship between drug and metabolite levels and between genotype and clin. response were investigated. Although the no. of responders in this study is insufficient for definite conclusions to be drawn, a target therapeutic concn. ranging from 195-400 .mu.g/L for the sum of venlafaxine and O-desmethylvenlafaxine is suggested. The ratio of O-desmethylvenlafaxine to venlafaxine in the serum concns. is a measure of metabolic turnover, and can be used to distinguish between ultrarapid and poor metabolizers. All but one of the nonresponders in this study had lower ratios than the responders. Three patients (9%) had homozygous defective CYP2D6 alleles and did not readily metabolize venlafaxine to O-desmethylvenlafaxine, pointing to poor metab. In these patients, N-desmethylation was increased. Two out of four patients detected by the ratio as potentially ultrarapid metabolizers were shown to have multiple copies of a functional CYP2D6 gene.

RE.CNT 18 THERE ARE 18 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

AB Thirty-three patients with **depression** treated with 225 mg venlafaxine were genotyped for the polymorphic enzyme, debrisoquine 4-hydroxylase (CYP2D6). The relationship between drug and metabolite levels and between genotype and clin. response were investigated. Although the no. of responders in this study is insufficient for definite conclusions to be drawn, a target therapeutic concn. ranging from 195-400 .mu.g/L for the sum of venlafaxine and O-desmethylvenlafaxine is suggested. The ratio of O-desmethylvenlafaxine to venlafaxine in the serum concns. is a measure of metabolic turnover, and can be used to distinguish between ultrarapid and poor metabolizers. All but one of the nonresponders in this study had lower ratios than the responders. Three

patients (9%) had homozygous defective CYP2D6 alleles and did not readily metabolize venlafaxine to O-desmethylvenlafaxine, pointing to poor metab. In these patients, N-desmethylation was increased. Two out of four patients detected by the ratio as potentially ultrarapid metabolizers were shown to have multiple copies of a functional CYP2D6 gene.

IT **93413-62-8**, O-Desmethylvenlafaxine 149289-30-5, N-Desmethylvenlafaxine
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(serum concns. of venlafaxine and metabolites in humans and CYP2D6 genotype)

L4 ANSWER 8 OF 11 CAPLUS COPYRIGHT 2002 ACS
AN 1998:375348 CAPLUS
DN 129:144527
TI Distribution and excretion of venlafaxine and O-desmethylvenlafaxine in human milk
AU Ilett, K. F.; Hackett, L. P.; Dusci, L. J.; Roberts, M. J.; Kristensen, J. H.; Paech, M.; Groves, A.; Yapp, P.
CS Department of Pharmacology, University of Western Australia, Nedlands, 6907, Australia
SO British Journal of Clinical Pharmacology (1998), 45(5), 459-462
CODEN: BCPHBM; ISSN: 0306-5251
PB Blackwell Science Ltd.
DT Journal
LA English
AB To characterize the transfer of venlafaxine (V) and its O-desmethyl metabolite (ODV) into human milk by measuring milk/plasma (M/P) ratio, and to est. the likely dose received by a breast-fed infant. Milk and plasma samples were collected from three lactating women who were taking venlafaxine for **depression**, and were at steady-state. In two of the patients, venous blood and milk samples were collected 0, 1, 2, 3, 4, 6, 8 and 12 h post dose, while in the third patient a single pair of blood and milk samples was obtained 0.83 h post dose. A plasma sample was obtained from each of their infants. V and ODV were measured in plasma and milk by high performance liq. chromatog. M/P was calcd. and infant dose estd. as drug concn. in milk .times. a milk intake of 0.15 l kg-1 day-1, relative to the wt.-adjusted maternal dose. Mean M/P for V was 4.1 (range 2.8-4.8) and 3.1 for ODV (range 2.8-3.8). The mean total infant dose (as V equiv.) was 7.6% (range 4.7-9.2%) of the maternal wt.-adjusted dose, with approx. equal amts. of V (3.5%) and ODV (4.1%) in the dose. ODV (median 100 .mu.g l-1) was detected in the plasma of all three infants. The infants were healthy and showed no acute adverse effects. These preliminary data show that the total dose of V and ODV ingested by breast-fed infants can be as high as 9.2% of maternal intake. Moreover there were measurable concns. of ODV in the infants' plasma. We recommend that exposed infants should be obsd. closely.
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IT **93413-62-8**, O-Desmethylvenlafaxine
RL: BPR (Biological process); BSU (Biological study, unclassified); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative); PROC (Process)
(distribution and excretion of venlafaxine and O-desmethylvenlafaxine in human milk)

L4 ANSWER 9 OF 11 CAPLUS COPYRIGHT 2002 ACS
AN 1998:340269 CAPLUS
DN 129:76011
TI The influence of cimetidine on the disposition kinetics of the antidepressant venlafaxine
AU Troy, Steven M.; Rudolph, Richard; Mayersohn, Michael; Chiang, Soong T.
CS Wyeth-Ayerst Research, Philadelphia, PA, 19101, USA
SO Journal of Clinical Pharmacology (1998), 38(5), 467-474
CODEN: JCPCBR; ISSN: 0091-2700
PB Lippincott-Raven Publishers
DT Journal
LA English
AB The influence of cimetidine on the disposition pharmacokinetics of the antidepressant drug venlafaxine and its active metabolite, O-demethylvenlafaxine, was examd. in healthy young men and women. The steady-state pharmacokinetic profiles of venlafaxine and O-demethylvenlafaxine were evaluated during a 24-h period after 5 days of treatment with venlafaxine (50 mg 3 times a day) and during a 2nd 24-h period after 5 days of combination treatment with venlafaxine (50 mg 3 times a day) and cimetidine (800 mg once a day). The apparent oral clearance of venlafaxine decreased and the av. steady-state plasma concn. of venlafaxine increased in the presence of cimetidine, but there were no changes in the corresponding concns. of the active metabolite. However, O-demethylvenlafaxine has a pharmacol. activity that is approx. equipotent to that of venlafaxine, and the sum of plasma venlafaxine plus O-demethylvenlafaxine concns. was increased by an av. of only 13%. Therefore, the effect of cimetidine coadministration is not expected to result in clin. important alterations in the response to venlafaxine in patients with **depression**. This may not be true, however, for patients with compromised hepatic metabolic function.
AB The influence of cimetidine on the disposition pharmacokinetics of the antidepressant drug venlafaxine and its active metabolite, O-demethylvenlafaxine, was examd. in healthy young men and women. The steady-state pharmacokinetic profiles of venlafaxine and O-demethylvenlafaxine were evaluated during a 24-h period after 5 days of treatment with venlafaxine (50 mg 3 times a day) and during a 2nd 24-h period after 5 days of combination treatment with venlafaxine (50 mg 3 times a day) and cimetidine (800 mg once a day). The apparent oral clearance of venlafaxine decreased and the av. steady-state plasma concn. of venlafaxine increased in the presence of cimetidine, but there were no changes in the corresponding concns. of the active metabolite. However, O-demethylvenlafaxine has a pharmacol. activity that is approx. equipotent to that of venlafaxine, and the sum of plasma venlafaxine plus O-demethylvenlafaxine concns. was increased by an av. of only 13%. Therefore, the effect of cimetidine coadministration is not expected to result in clin. important alterations in the response to venlafaxine in patients with **depression**. This may not be true, however, for patients with compromised hepatic metabolic function.
IT **93413-62-8**, O-Desmethylvenlafaxine

RL: BPR (Biological process); BSU (Biological study, unclassified); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative); PROC (Process)
(cimetidine effect on the disposition kinetics of venlafaxine in humans, with formation of)

L4 ANSWER 10 OF 11 CAPLUS COPYRIGHT 2002 ACS
AN 1997:681434 CAPLUS
DN 127:355027
TI Application of a first-pass effect model to characterize the pharmacokinetic disposition of venlafaxine after oral administration to human subjects
AU Taft, David R.; Iyer, Ganesh R.; Behar, Leon; DiGregorio, Robert V.
CS Division of Pharmaceutics and Industrial Pharmacy, Long Island University, Brooklyn, NY, 11201, USA
SO Drug Metabolism and Disposition (1997), 25(10), 1215-1218
CODEN: DMDSAI; ISSN: 0090-9556
PB Williams & Wilkins
DT Journal
LA English
AB Venlafaxine (VEN), a drug used in the treatment of **depression**, undergoes significant first-pass metab. after oral dosing to O-desmethylvenlafaxine (ODV), a metabolite with comparable therapeutic activity to that of parent drug. The pharmacokinetic disposition of VEN was characterized using a "first-pass" model that incorporates a presystemic compartment (liver) to account for the first-pass metab. of VEN to ODV. A series of differential equations were simultaneously fitted to plasma concns. of parent and metabolite. A good fit of the model to obsd. data was demonstrated, generating ests. for the following parameters: ka (1.31 h-1), VVEN (252 L), CLint (65.8 L/h), RL (liver:plasma partition coeff., 29.6), VODV (181 L), and CLODV (23.5 L/h). Parameter ests. correlated closely with those obtained through noncompartmental methods. These results indicate that the time-course disposition of a compd. undergoing first-pass hepatic metab. after oral dosing can be successfully modeled.
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IT **93413-62-8**, O-Desmethylvenlafaxine
RL: BPR (Biological process); BSU (Biological study, unclassified); MFM (Metabolic formation); THU (Therapeutic use); BIOL (Biological study); FORM (Formation, nonpreparative); PROC (Process); USES (Uses)
(application of a first-pass effect model to characterize the pharmacokinetic disposition of venlafaxine after oral administration to human subjects)

L4 ANSWER 11 OF 11 CAPLUS COPYRIGHT 2002 ACS
AN 1996:444791 CAPLUS
DN 125:107239
TI Two fatal cases of venlafaxine poisoning

CAPLUS ONLINE PRINTOUT

AU Parsons, Ann T.; Anthony, Robert M.; Meeker, James E.
CS Laboratory Forensic Services, Sacramento, CA, 95820, USA
SO J. Anal. Toxicol. (1996), 20(4), 266-268
CODEN: JATOD3; ISSN: 0146-4760
DT Journal
LA English
AB Venlafaxine is a phenethylamine deriv. that has recently been approved for use in the treatment of **depression**. It is chem. unrelated to tricyclic, tetracyclic, or other available antidepressant agents. Anticholinergic, hypotensive, hypertensive, and cardiotoxic side effects are rare. Two fatal cases encountered at sep. labs. are discussed, both involving high levels of venlafaxine. The concns. of the drug in peripheral blood, heart blood, urine, vitreous humor, and liver are reported. Descriptions of extn. and gas chromatog. methods for confirmation and quantitation are included.
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IT **93413-62-8**, O-Desmethylvenlafaxine 93413-69-5, Venlafaxine
RL: ANT (Analyte); ANST (Analytical study)
(tissue distribution of venlafaxine and its metabolite in humans after fatal poisoning)

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CAPLUS ONLINE PRINTOUT

AN 1997:681434 CAPLUS
DN 127:355027
TI Application of a first-pass effect model to characterize the pharmacokinetic disposition of venlafaxine after oral administration to human subjects
AU Taft, David R.; Iyer, Ganesh R.; Behar, Leon; DiGregorio, Robert V.
CS Division of Pharmaceutics and Industrial Pharmacy, Long Island University, Brooklyn, NY, 11201, USA
SO Drug Metabolism and Disposition (1997), 25(10), 1215-1218
CODEN: DMDSAI; ISSN: 0090-9556
PB Williams & Wilkins
DT Journal
LA English
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IT **93413-62-8**, O-Desmethylvenlafaxine
RL: BPR (Biological process); BSU (Biological study, unclassified); MFM (Metabolic formation); THU (Therapeutic use); BIOL (Biological study); FORM (Formation, nonpreparative); PROC (Process); USES (Uses)
(application of a first-pass effect model to characterize the pharmacokinetic disposition of venlafaxine after oral administration to human subjects)